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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/453,801	12/03/1999	Saswati Chatterjee	1954-287	3067

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EXAMINER	
LEFFERS JR, GERALD G	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 06/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/453,801	CHATTERJEE ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr., PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,13-15,17,18,22 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,13-15,17,18,22 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 4-1-04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/1/2004 has been entered.

In the amendment filed 4/1/2004 claim 1 was amended and claims 8-10 were cancelled without prejudice. Claims 1-5, 13-15, 17-18 and 22-23 are pending in the instant application and under consideration.

Any objection to the specification or rejection of record in the previous office actions that is not addressed herein is withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 13-15, 17-18 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection, necessitated by applicants' amendment of the claims in the papers filed 4/1/2004.**

Each of the rejected claims comprises a newly added limitation reciting a specific levels of stem cell factor (i.e. "about" 1 ng/ml SCF). There is no literal or inherent support for this limitation in the originally filed claims and specification. Therefore, this limitation is impermissible NEW MATTER.

Claim 23 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for embodiments wherein the hematopoietic cells in the G0 phase of the cell cycle are maintained under conditions where IL-3, IL-6 and cell stimulating factor (CSF) are present, and where cytokine levels are no greater than about 15 ng/ml IL-3, 15 ng/ml IL-6 and 1.5 ng/ml of granulocyte-macrophage colony stimulating factor (GMCSF), does not reasonably provide enablement for embodiments where IL-3, IL-6 and CSF are not present, or where IL-3, IL-6 and GMCSF are at higher than the cited levels. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. **This rejection is maintained for reasons of record in the office actions mailed 12/18/02 and 12/2/2003, and repeated below.**

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The nature of the invention is extraordinarily complex, involving the difficult purification of hematopoietic stem cells (e.g. $CD34^{+++}$ $CD38^{-}$ cells) that are in the G0 phase of the cell cycle and maintaining/transducing the cells in such a manner that the cells remain in the G0 phase of the cell cycle, and wherein the transferred DNA remains stably integrated into the genome of the hematopoietic stem cells for at least 4 weeks.

Breadth of the claims: The claimed methods are very specific in that the methods are necessarily performed on hematopoietic stem cells that are in the G0 phase of the cell cycle. However, the claims are broadly drawn with regard to the cell culture conditions required to maintain the hematopoietic stem cells in the G0 cell-cycle state.

Guidance of the specification: The specification teaches that there are essentially two main critical elements of the claimed methods: 1) purification of the extremely rare hematopoietic stem cells that are in the general cell population and are in the G0 phase of the cell cycle, and 2) maintaining the cells such that the purified hematopoietic stem cells remain in the G0 phase of the cell cycle at least during transduction.

With regard to the first element, the applicants utilized a 3-step approach to isolating a sufficiently large number of purified hematopoietic stem cells in G0 for transduction to have a reasonable chance of success. This 3-step approach involved initial purification of $CD34^{+}$ cells from mononuclear cells with Multineyi columns, followed by flow sorting of the $CD34^{+}$ population based upon DNA and RNA content to segregate out only those $CD34^{+}$ cells which were in the G0 phase, and finally, sorting of the resulting cell population to obtain those cells which were $CD34^{+}$ and $CD38^{-}$ (e.g. pages 16-17 of the instant specification; Chatterjee 1.132 Declaration, paragraph 6). The

specification teaches that other suitable methods are known in the art for obtaining sufficient numbers of purified hematopoietic stem cells at G0 for transfection (e.g. page 17, line 11 of the instant specification).

With regard to the conditions for maintaining the cells in the G0 state, the specification teaches that under the conditions of the methods of the invention, with particular regard for low cytokine levels, the hematopoietic stem cells in culture remain quiescent for up to 2 days. The specification teaches that in order to perform the method, low levels of the cytokines IL-6, IL-3 and GMCSF are important and that the higher the cytokine levels, the more the cells are stimulated to undergo mitosis. Alternatively, the cells will die if the levels of the recited factors are too low. For these reasons, the specification teaches that it is advantageous to use cytokine levels of no greater than 15 ng/ml IL-3, 15 ng/ml IL-6, and 1.5 ng/ml of GMCSF (e.g. pages 13-14 of the instant specification). There are no teachings in the instant specification for practicing the claimed methods with culture conditions where IL-3, IL-6 and SCF are not present, or where IL-3, IL-6 and GMCSF are present at levels greater than about 15 ng/ml IL-3, 15 ng/ml IL-6 and 1.5 ng/ml GMCSF.

The existence of working examples: There are no working examples in the instant specification for practicing the claimed methods with culture conditions where IL-3, IL-6 and SCF are not present, or where IL-3, IL-6 and GMCSF are present at levels greater than about 15 ng/ml IL-3, 15 ng/ml IL-6 and 1.5 ng/ml GMCSF.

State of the art: The state of the art with regard to maintaining extremely primitive hematopoietic cells at the G0 phase of the cell cycle at the time of applicants' invention was underdeveloped. In her declaration filed under 1.132 to overcome the

prior art (Paper No. 10, filed 1/17/02), Dr. Saswati Chatterjee, one of the instant inventors, states that prior to the instant invention, transduction of extremely primitive, G0, quiescent, pluripotent stem cells had not been demonstrated. Dr. Chatterjee makes clear that the levels of cytokines in the cell culture are critical to maintaining the cells at G0. For instance, Dr. Chatterjee states that the conditions taught by Zhou et al, with relatively high levels of IL-3 and GMCSF, would result in mitosis and loss of the G0 cell cycle status (page 7, paragraph 11). Alternatively, according to Dr. Chatterjee, even if the factors IL-3, IL-6 and GMCSF are present at the levels indicated in the instant specification as being within the optimal range (i.e. IL-3, 10ng/ml; IL-6, 5ng/ml and GMCSF at 1ng/ml), these factors are not art recognized as being enough to support stem cells. Dr. Chatterjee distinguishes, at least in part, the methods of the instant invention over previous work done by applicants' group, Fisher-Adams et al, based on the observation that cell stimulating factor was present in the methods of the instant specification and was critical for supporting survival of the hematopoietic stem cells (paragraph 9, Paper No. 10).

Predictability of the art: Given the teachings of the instant specification with regard to the difficulties of maintaining the hematopoietic stem cells in the G0 state without inducing mitosis and still maintaining survival, the lack of teachings or working examples in the instant specification or prior art where hematopoietic stems cells are maintained and transduced in culture with culture conditions other than those recited above, practicing the claimed methods with cytokine levels and compositions other than those indicated above would have been unpredictable. One of skill in the are would have had to resort to unpredictable, trial-and-error experimentation in order to develop

culturing/transduction conditions where IL-3, IL-6 or SCF were not present, or where cytokine levels are greater than about 15 ng/ml IL-3, 15 ng/ml IL-6 and 1.5 ng/ml of granulocyte-macrophage colony stimulating factor (GMCSF).

The amount of experimentation necessary: Based on the consideration of all of the factors outlined above, it would have required undue, unpredictable experimentation to practice the claimed methods where IL-3, IL-6 or SCF were not present, or where cytokine levels were greater than about 15 ng/ml IL-3, 15 ng/ml IL-6 and 1.5 ng/ml of GMCSF. Therefore, the instant specification is not considered enabling for the full scope of the broadly claimed invention.

Response to Arguments

Applicant's arguments filed in the papers filed 4/1/2004 essentially do not address rejection of claim 23, which does not recite any specific limitations with regard to specific cytokine levels, but still requires the stable integration of an AAV vector into the genome of multi-potential $CD34^{+++}CD38^{-}$ cells in the G0 phase of the cell cycle for at least 4 weeks. The response presents no arguments as to why the particular levels of IL-3, IL-6 and SCF are not required in order to practice the claimed method.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 1-5, 13-15, 17-18 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This is a new rejection, necessitated by applicants' amendment of the claims in the response filed 4/1/2004.**

Each of the claims recite a limitation that stem cell factor (SCF) is present in the culture media at a concentration of "about" 1 ng/ml. There is no explanation provided by the specification as to what constitutes a concentration of "about" 1 ng/ml. Therefore, the skilled artisan would not be able to recognize when they have infringed the recited invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (571) 272-0772. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

GERRY LEFFERS
PRIMARY EXAMINER

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